

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 004979-00050	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2005/012113	International filing date (<i>day/month/year</i>) 11 April 2005 (11.04.2005)	Priority date (<i>day/month/year</i>) 09 April 2004 (09.04.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PRESIDENT AND FELLOWS OF HARVARD COLLEGE		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 <i>bis</i> .1(a).																								
2.	This REPORT consists of a total of 5 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 80%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
<input checked="" type="checkbox"/>	Box No. I	Basis of the report																							
<input type="checkbox"/>	Box No. II	Priority																							
<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability																							
<input type="checkbox"/>	Box No. IV	Lack of unity of invention																							
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																							
<input type="checkbox"/>	Box No. VI	Certain documents cited																							
<input type="checkbox"/>	Box No. VII	Certain defects in the international application																							
<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application																							
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44 <i>bis</i> .3(c) and 93 <i>bis</i> .1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44 <i>bis</i> .2).																								

<p style="text-align: center;">The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. +41 22 338 82 70</p>	<p>Date of issuance of this report 11 October 2006 (11.10.2006)</p> <p>Authorized officer Athina Nickitas-Etienne</p> <p>e-mail: pt04@wipo.int</p>
--	--

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ERNEST V. LINEK
28 STATE STREET - 28TH FLOOR
BOSTON, MA 02109

PCT

REC'D 21 OCT 2005

WIPO

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **19 OCT 2005**

Applicant's or agent's file reference

004979-00050

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US05/12113

International filing date (day/month/year)

11 April 2005 (11.04.2005)

Priority date (day/month/year)

09 April 2004 (09.04.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07D 491/044, 491/10, 263/10; C07C 229/30; C07F 7/02 and US Cl.: 548/110, 237, 406, 411, 453; 560/170

Applicant

PRESIDENT AND FELLOWS OF HARVARD COLLEGE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-8300

Authorized officer

Anthony J. Pavigliani

Telephone No. (571) 272-3107

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US05/12113

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/12113

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>1 - 45</u>	YES
	Claims <u>NONE</u>	NO
Inventive step (IS)	Claims <u>1 - 45</u>	YES
	Claims <u>NONE</u>	NO
Industrial applicability (IA)	Claims <u>1 - 45</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1 - 45 meet the criteria set out in PCT Article 33(2)-(3), and possess novelty and an inventive step, because the prior art does not teach or fairly suggest the compounds of Formula (Ia), Formula (IIa), or Formula (IIIa) ("salinosporamide" and "lactacystin" derivatives), as depicted in **Claims 1, 9 and 17**, respectively. In addition, the synthetic intermediates claimed in **Claims 26 - 44**, while similar to several intermediates used in making related compounds, were neither directly disclosed or fairly suggested by the prior art, and thereby possess novelty and an inventive step as well. **Claim 45**, which recites a compound that is limited by a specific stereoisomeric configuration, is not found in the prior art or fairly suggested by it, and so possesses novelty and an inventive step.

Claims 1 - 25 are free of the prior art in part because the compounds of Formula (Ia), Formula (IIa) and Formula (IIIa) require the substituent "**R**³" at the 4-position of the pyrrolidine ring to be an alkyl, alkenyl, alkynyl, cycloalkyl, etc., while the compounds disclosed in the prior art have only a hydrogen atom at that site. The difference in substitution at this site is significant for the molecule's biological activity and its stability: as noted by authors E.J. Corey and Z.L. Wei-Dong in their article in *Tetrahedron Letters*, "most of the structural features of the [lactacystin molecule] are critical to its activity...the hydroxy at C(6) must be *cis*...for proteasome inactivation...removal of the methyl substituent at [the adjacent site on the ring] strongly reduces bioactivity...and also leads to chemical instability resulting from facile elimination of the hydroxyl at [the **R**³ site]..." Corey, E., and Wei-Dong, Z., "An Efficient Total Synthesis of a New and Highly Active Analog of Lactacystin," *Tetrahedron Letters*, vol. 3941, pages 7475-7478 (Oct. 1998), at page 7475, especially at lines 15 - 19. Thus the substitution of an alkyl, alkenyl, alkynyl, or cycloalkyl group at the **R**³ site on the pyrrolidine ring would not be anticipated or fairly suggested by compounds in the prior art which have a hydrogen atom at that site, as the stability and biological activity of the molecule would not be predictable as related to the known compounds; therefore, the claimed compounds possess novelty and an inventive step over the prior art.

Claims 1 - 45 all meet the criteria set out in PCT Article 33(4), and thus satisfy the requirement for industrial applicability, because the subject matter claimed in **Claims 1 - 45** can be made or used in industry.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US05/12113

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 26 - 44 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 as indefinite for the following reason(s): **Claims 26 - 44** each refer to "Scheme 2" or "Scheme 3" in the Specification, but neither Scheme is recited in the claims.